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Supplemental Submission in Support of Citizen Petition and Petition for Stay, Docket Nos. 2004P-0140/CP1 and 2004P-0140/PSA 1 and Opposing Petition for Stay Docket No. 2004P-0140/PSA 2

On behalf of King Pharmaceuticals, Inc., ("King") the undersigned hereby make this supplemental submission in support of King's Citizen Petition and Petition for Stay, in response to the comments submitted by Corepharma LLC ("Core"), and in response to the supplemental submission by Mutual Pharmaceutical Co., Inc. ("Mutual") in support of its Petition for Stay. This supplemental submission is supported by declarations from Leslie Z. Benet, Ph.D., an expert in clinical pharmacology (Exhibit 1), Jerome P. Skelly, Ph.D., an expert in biopharmaceutics and pharmacokinetics (Exhibit 2), and Michael E. Elia, M.D.,

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an orthopedic surgeon who regularly prescribes SKELAXIN®, as well as other drugs for pain management (Exhibit 3).[1]

Introduction

Core's comments are comprised of a litany of entirely unsupported assertions. They do not include *any* actual clinical data demonstrating that omission of the food effect information from its product's labeling will have no effect on the safe and effective use of the product. The declaration of Dr. Bass similarly provides arguments, but no data. Essentially, Core's and Dr. Bass' position is that metaxalone is a wonder drug that is equally safe and effective at any dose. This is inconsistent with the various legal prerequisites for approval of ANDAs, *e.g.,* the requirement that bioequivalence be shown to a previously approved reference listed drug ("RLD"), the requirement that bioquivalence be shown to the RLD in both fed and fasting conditions if a food effect has been demonstrated, and the requirement that generic drug labeling copy the label of the RLD and not be based on a self-serving second guess by a generic applicant as to what parts of the prescribing information approved by FDA for the pioneer drug are "really" significant. Core's unsupported arguments do not satisfy its burden of

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1 For clarity, the declarations of Drs. Benet and Elia that are attached to this submission will be referenced as "Benet Decl. 2", and "Elia Decl. 2" to distinguish them from the declarations submitted with King's March 18, 2004 Citizen Petition. Dr. Skelly's declaration will be referenced as "Skelly Decl."

establishing that its generic product with the incomplete and 'inequivalent' labeling proposed by Core is as safe and effective as the RLD, SKELAXIN®. Accordingly, FDA should not accept a section viii statement from generic applicants and should not permit removal from generic metaxalone labeling of the pharmacokinetics information that appears in the SKELAXIN® labeling.

Mutual's submission likewise consists solely of speculative arguments designed to interfere with and delay FDA's review of King's labeling supplement. Mutual has submitted no relevant data or other evidence to support its view that the reviewing division acted improperly in issuing its approvable letter or to support a reversal of the determination reflected in that letter or any stay of FDA's decision regarding King's labeling supplement.

I. The Historical Marketing of SKELAXIN® Without Labeling Describing A Food Effect Is Irrelevant

The history of safe and effective use of metaxalone during a time when the label did not address food effects is irrelevant to the question of whether, now that food effects are known, they must be described in the labels for both SKELAXIN® and any generic metaxalone products. *See* Benet Decl. 2, ¶¶ 6-9. Core repeatedly emphasizes that the SKELAXIN® label did not historically describe a food effect or recommend dosing with or without food, yet Core fails to acknowledge the obvious – the information was not included because the information was not known. Now that it is known, the text of the former label

provides no basis to conclude that the information is irrelevant or can be properly omitted from labeling for generic metaxalone products.[2]

An ANDA is not approvable based on a mere assertion that the product would be "safe enough" or "effective enough" with old labeling written before new information, such as a food effect, was discovered. Instead, the key question is whether the generic product will be equally as safe and effective as the RLD – a conclusion that can be based only on the combination of bioequivalence and labeling equivalence – or a clinical showing that differences in labeling do not affect safety or effectiveness. Benet Decl. 2, ¶ 9. Deviations are not justified simply because the ANDA applicant wishes that new information properly appearing in the labeling of the RLD had not been discovered, or had not been covered by FDA regulations that require such information to appear in labeling, or had not been explicitly approved by FDA for inclusion in the labeling.

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2 Core seems to believe that new information in a product label is unimportant, unnecessary, and should be ignored by FDA unless that new information addresses a specific, identifiable, serious safety or efficacy problem. Core ignores a huge category of post-approval label changes that do not "correct" any specific and serious problem, but, rather, contribute to a better understanding of the drug and therefore enhance its safe and effective use. Indeed, whole categories of approved labeling information, such as animal safety data, clinical study data, pharmacokinetic data, and information about special populations such as pregnant, geriatric and pediatric populations, and persons with renal or hepatic deficiencies, consist largely of information that are believed potentially to bear on prescribing decisions or on individual dosage and administration instructions but which do not necessarily correlate to specific, proven, clinically significant differences in effect.

Instead, ANDAs that deviate from conditions of approval and labeling of the RLD are approvable *only* based on a showing that the deviations do not negatively impact the safe and effective use of the drug – and this showing cannot simply be based on reference to the prior marketing of the product without the new information. Indeed, Core's repeated appeals to the previous clinical data generated with SKELAXIN®, and the history of clinical use of that product, simply underscore the fact that Core, as a generic applicant, seeks to rely on these data as a basis for approval to market its own product and can do so *only* if Core demonstrates equivalence to SKELAXIN® in all of these respects. Moreover, as Dr. Benet observed in his original declaration and reiterates in his second declaration, marketing history provides no reliable information upon which to make science-based regulatory judgments, as problems are uncovered as science progresses. *See* Benet Decl. 2, ¶¶ 7-8; Exhibit 10 to King's March 18, 2004 Citizen Petition, ¶ 28. Here, science has progressed beyond the old labeling and information upon which Core relies, and Core's request that the Agency ignore this progress and 'live in the past' is irresponsible.

Finally, the fact that the scientific literature includes sporadic references to daily doses significantly higher than those recommended in SKELAXIN® labeling does not relieve Core of its burden to demonstrate that its product with 'inequivalent' labeling would be as safe and effective as the RLD. The question is

not whether the plasma concentrations observed following a high-fat meal are safe; neither King nor anyone else has suggested they are unsafe. Instead, the question is whether providing information regarding the observed food effect enhances the safe and effective use of SKELAXIN® – by, for instance, aiding practitioners in selecting the correct dosage and administration for their individual patients – and therefore omission of this information from the labeling for generic metaxalone would render the generic product less safe or effective than SKELAXIN®.[3] As established in King's Citizen Petition, the answer to this question is yes.

II. King's Data Demonstrate A Significant Food Effect

A. King's Studies Were Appropriately Designed And Conducted

Core criticizes King's studies as conducted under "exaggerated conditions" resulting in "artificially high" increases in bioavailability that have no actual or practical effect. According to Core, the data are irrelevant and should be ignored because the studies were single-dose studies in which metaxalone was administered with a high-calorie, high-fat meal. Similarly, Mutual complains that

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3 Core also suggests that studies conducted with Robins' participation confirmed that the recommended daily dose is 800 mg three to four times a day, both when administered with food and when administered without food. Core seriously mischaracterizes the cited studies. All pre-date (by decades) the discovery of the food effect, and none were designed to investigate food effects. Moreover, none discusses any observed (or hypothetical) food effect. Indeed, not one of the cited articles (Exhibits 3, 4, or 10 to Core's submission) includes any evidence that metaxalone was actually administered with food. As such, these studies "confirm" nothing of relevance to King's Petitions. They certainly do not meet Core's burden of proving that there is no potential clinical significance to the food effect.

King's studies are deficient because they did not investigate the effects of various different types of meals (*e.g.,* low-carbohydrate, vegetarian, diabetic) or varying eating patterns for individuals (*e.g.,* low-fat breakfast, followed by a high-fat lunch, followed by a low-fat dinner). Incredibly, Mutual seems to advocate the view that food effect data is irrelevant and should not be shared with practitioners unless and until studies are conducted documenting the effect on bioavailability of *all* types of meal combinations a patient might possibly consume.

As an initial matter, the studies were conducted in accordance with FDA's guidance, as Core acknowledges elsewhere in its submission.[4] In the words of Dr. Skelly, FDA's former Director and Program Manager for Biopharmaceutics and Deputy Director of CDER's Office of Research and Associate Director (for Science) in the Office of Generic Drugs:

> Based on my experience at FDA and as a pharmacokineticist, it is my opinion that, contrary to Core and Mutual's criticisms, King's clinical studies -- Studies 101, 103, 105 and 106 -- were designed and conducted in a scientifically appropriate manner, fully consistent with FDA's Guidance for Industry, *Food-Effect Bioavailability and Fed Bioequivalence Studies*, FDA, CDER (Dec. 2002), and the Agency's predecessor draft guidance. . . . Thus, in my opinion, any suggestion that the utilization of the high-fat meal renders the clinical studies useless and of no practical or clinical import is contrary to FDA policy and unjustified. In particular, it is my opinion that this alleged defect in the clinical study protocol is

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4 *See Guidance for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies,* CDER (Dec. 2002), available at: http://www.fda.gov/cder/guidance/5194fnl.doc; *see also Guidance for Industry, Food-Effect Bioavailability and Bioequivalence Studies* (Draft), CDER (Oct. 1997) (Core Exhibit 19).

> certainly no basis for asserting that the omission of the pharmacokinetic data from the clinical studies would be proper.

Skelly Decl., ¶ 41, 45; *see also id.,* ¶ 43 ("the FDA guidelines recommend that food-effect bioavailability studies and fed bioequivalence studies be conducted using the standardized high-fat meal . . . Indeed, if the caloric breakdown of the meal significantly differs from the prescribed standardized high-fat meal, a scientific rationale for the difference is required").

FDA's guidance was initially prepared by experts within the Agency[5] and was finalized over a number of years after considering comments on the draft published in 1997.[6] The Agency has repeatedly confirmed that single-dose food effect studies in which high-fat meals are utilized provide important data that should be included in product labeling. *See, e.g.,* approved labeling for Prempro™, Sustiva®, Invirase®, Glucotrol XL®, Rebetron™, and Cordarone®; *see also* Skelly Decl., ¶¶ 41, 48. Indeed, when FDA requires fed bioequivalence studies for ANDA approval (as is the case for metaxalone), the studies required are

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5 Specifically, the Food-Effect Working Group of CDER's Biopharmaceutics Coordinating Committee. *See Guidance for Industry, Food-Effect Bioavailability and Bioequivalence Studies* (Draft), CDER at n. 1 (Oct. 1997) (Core Exhibit 19).

6 *See Reports and guidance documents; availability, etc.: Food-effect bioavailability and bioequivalence studies; industry guidance,* 62 Fed. Reg. 67879 (Dec. 30, 1997) (announcing availability of draft guidance and inviting comments); *Guidance for Industry on Food-Effect Bioavailability and Fed Bioequivalence Studies; Availability,* 68 Fed. Reg. 5024 (Jan. 31, 2003) ("Based on comments received on the draft guidance and the refinement of agency thinking on the conduct of such studies, FDA has revised the guidance").

single-dose, high-fat intervention studies.[7] Skelly Decl., ¶ 43. Core's and Mutual's unsupported assertion that the Agency essentially 'got it wrong,' and has 1) published guidance to recommend, 2) approved labeling to discuss, and 3) required ANDA applicants to conduct useless studies with no practical import is simply untenable. Rejection of King's data now, based on alleged defects in the protocol, would constitute a dramatic reversal of long-standing Agency policy.

Moreover, Core's position that, when metaxalone is administered 3-4 times a day as recommended in product labeling, the difference between fed and fasted blood levels will substantially decrease to the point of clinical insignificance is incorrect as a scientific matter. As Dr. Benet explains, Core and its expert are "simply wrong:"

> Regardless of whether metaxalone is administered as a single dose or in multiple doses, if there is an increase in bioavailability in the fed state as compared to fasted state, that change in bioavailability will be present when multiple doses are taken. The increase in bioavailability will not diminish just because more than one dose is administered and steady-state is achieved.

Benet Decl. 2, ¶ 23; *see also id.*, ¶ 24; Skelly Decl., ¶ 48.[8]

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7 Core's argument that differences in bioavailability when metaxalone is administered with and without food can simply be ignored contradicts the requirement that bioequivalence be shown and, once food effects are observed, that bioequivalence be shown in both fasted and fed conditions. Simply put, Core's argument, if accepted, eviscerates the core Hatch-Waxman criteria for generic drug approval. Contrary to Core's suggestion, this concern is not simply theoretical – by determining that food effect information may be omitted from generic labeling, FDA would be simultaneously reversing its determination that bioequivalence of metaxalone must be shown in fed as well as fasting conditions. *See* Skelly Decl., ¶¶ 36, 37.

8 Core and its expert also overlook the possibility that some patients will never achieve steady-state, depending on the prescribing physician's response to their individual needs. For

Core also wrongly assumes that a direct linear correlation between fat intake and bioavailability of metaxalone has been shown. To King's knowledge, no data establishing such a correlation exist, and certainly Core has not submitted any support for this assumption. Mutual's related contention that the bioavailability with metaxalone will necessarily vary materially, depending on the type of meal with which it is ingested, is also unsupported.[9] *See* Benet Decl. 2, ¶ 18-22; Skelly Decl., ¶ 46, 42. Absent additional data on blood levels following co-administration of metaxalone with a wider range of meals, it is impossible to conclude that the high-fat breakfast used in King's studies contains the optimal amount of fat to maximize metaxalone bioavailability. *See* Skelly Decl., ¶ 46 ("Co-administration with different meals may *or may not* impact bioavailability differently than co-administration with the standard high fat meal"). Accordingly, taking SKELAXIN® with lower fat meals (or other types of meals) may well result in an equally robust, or even greater, increase in plasma concentrations. *See* Benet Decl. 2, ¶¶ 19-21; Skelly Decl., ¶ 46.

Relatedly, Core and Mutual's speculation about additional clinical studies

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instance, Dr. Elia notes that if a patient complains of drowsiness that interferes with daily activities, it would not be uncommon for a physician to recommend that SKELAXIN® only be taken later in the day or at night. Elia Decl. 2, ¶ 7.

9 The studies cited by Mutual in support of this point involved entirely different drug substances, such as quinidine gluconate, cefaclor, cyclosporine, and fenretinide. These studies do not demonstrate anything with regard to the bioavailability of metaxalone. Benet Decl. 2, ¶ 19.

that could be conducted to investigate the impact on bioavailability of different types of meals has no bearing on the question of whether the currently-known food effects may properly be omitted from generic labeling:

> Core and Mutual also err in assuming that the *possibility* that bioavailability may be impacted differently when metaxalone is co-administered with different types of meals means that information on known food-effects should be omitted from generic metaxalone labeling. Contrary to Core and Mutual's suggestion, as discussed above, FDA has never required that all possible food effects be clinically investigated before information about known food effects is incorporated into product labeling.

Skelly Decl., ¶ 47. In short, in the absence of more clinical data investigating a wider range of meals, generated by Core or Mutual or anyone else, conjecture about what other clinical studies might show does not detract from the clear relevance of the information which actually exists.[10]

Finally, Core and its expert also err in assuming (without supporting data) that the standardized high-fat test meal differs significantly from the average American meal. Data indicate that Americans consume an average of 70-80 grams of fat per day, with men consuming, on average, more fat than women.[11] Notably,

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10 Core and Mutual also complain about the purportedly small number of subjects in King's studies. In fact, King's studies were appropriately sized, given their purpose, and are consistent, in terms of number of subjects, with other bioavailability studies, including those submitted by generic drug companies in support of ANDAs. Skelly Decl., ¶¶ 49, 51.

11 *See* Lori Beth Dixon and Nancy D. Ernst, *Choose a Diet That is Low in Saturated Fat and Cholesterol and Moderate in Total Fat: Subtle Changes to a Familiar Message*, J. of Nut., Supp., pp. 510S-526S (2001), at Table 3, attached hereto as Exhibit 4; National Health and

these data pre-date the tremendous increase in popularity of high-fat/low-carbohydrate diets, which advocate up to 100 grams or more of fat a day, with 55-65% of calories from fat.[12] Accordingly, fat intake, among a large and growing segment of the population, is now likely significantly higher than the 70-80 grams reported average. Indeed, even popular non-Atkins style meals are often high-fat. For example, a Big Mac® and large fries from McDonalds® contains 58 grams of fat; a Venti® café mocha (whole milk with whip cream) and a piece of classic coffee cake from Starbucks Coffee® contains 54 grams of fat; and a Classic Club salad with Honey Mustard dressing from Subway® contains 43 grams of fat.[13] Accordingly, the high-fat intervention studied by Elan/King is not only achievable,

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Nutrition Examination Survey, *Intake of Calories and Selected Nutrients for the United States Population, 1999-2000,* U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, attached hereto as Exhibit 4; Advance Data from Vital and Health Statistics, *Dietary Intake of Ten Key Nutrients for Public Health, United States: 1999-2000*, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, No. 334 (April 17, 2003), attached hereto as Exhibit 6.

12 Freedman, Marjorie R., King, Janet, and Kennedy, Eileen, *Popular Diets: A Scientific Review,* Obesity Research, Vol. 9, Suppl. 1, 1S-40S at 5S, 11S (March 2001), attached hereto as Exhibit 7; Volek, Jeff S., Ph.D., R.D., Westman, Eric C., M.D., MHS, *Very-low-carbohydrate weight-loss diets revisited,* Cleveland Clinic Journal of Medicine, Vol. 69, No. 11, 849-862 at 853-854 (Nov. 2002), attached hereto as Exhibit 8.

13 Nutrition information for various McDonalds®, Starbucks Coffee®, and Subway® menu items, including those discussed above, is available at: http://www.mcdonalds.com/app_controller.nutrition.categories.nutrition.index.html, http://www.starbucks.com/retail/nutrition_info.asp, and http://www.subway.com/applications/NutritionInfo/nutritionlist.aspx?CountryCode=USA&ID=salad, respectively.

but common, in the U.S. diet. Thus, Core is incorrect in suggesting that Americans are unlikely to achieve the plasma levels measured after consumption of SKELAXIN® with the standardized high-fat meal.

B. Individual Subject Data Provide No Basis To Question King's Studies

Core also complains that King's individual subject data reveal that fasted-state bioavailability levels can equal or exceed those experienced when metaxalone is administered with a high-fat meal. Core and its expert attribute this to the fact that the body performs enhanced digestive functions periodically, so if metaxalone is administered during this period (even without food) bioavailability will be enhanced. *See* Core comments, footnote 11; Bass Decl. ¶¶ 23, 46-47. As an initial matter, assuming *arguendo* that Core accurately describes this phenomenon, this digestive function would impact the bioavailability of all drugs. Benet Decl. 2, ¶ 25; Skelly Decl., ¶ 26. Despite this, FDA routinely approves labeling describing food effects based on average plasma responses across all study subjects. *See* Benet Decl. 2, ¶¶ 25-26.

Relatedly, picking apart a bioavailability study based on a *post hoc* reanalysis of individual subject data is inappropriate and misleading. BA/BE studies are designed to generate data on average and on relative deviation (a measure of variability between subjects). This is the basis on which FDA evaluates the results of such studies and has set corresponding approval criteria, including the bioequivalence criteria for the approval of generic drugs. If Core intends to suggest that individual subject variability in a bioequivalence study should be separately analyzed and, if significant, should provide a basis to reject the apparent results of the study, then it would follow that similar analyses should be conducted of the bioequivalence studies that Core and all other generic applicants rely on to "prove" the equivalence of their products to their brand name counterparts. We are certain that this is not Core's intent. The fact that it would make this argument, however, underscores the degree to which Core either fails to appreciate the inconsistencies in its position, or desires those inconsistencies to be overlooked.

III. King's Data Demonstrate Significant Age And Gender Effects

Core claims that King's age effect data show only a "trivial" increase in fasted bioavailability that is statistically insignificant. In fact, the results of Study 105, Study 106, and the meta-analysis reveal that, in the fed state, age has little or no effect upon the bioavailability of Skelaxin® – regardless of gender. In contrast,

in the fasted state, bioavailability was statistically significantly increased with an increase in age – also regardless of gender. Moreover, it is clear that the age-related variations in the bioavailability of metaxalone are minimized when SKELAXIN® is administered in the presence of food. Skelly Decl., ¶¶ 29-30. As Dr. Skelly explains:

> The data indicate that age is much more strongly associated with bioavailability in the fasted condition than in the fed condition, and Core and its expert fail to refute this fact. Based on the studies and the meta-analysis, it is clear that the estimated effect of age on AUC under fasted conditions is approximately three to four times larger than the estimated effect under fed conditions. The difference between the estimated effect of age on C_{max} under fasted vs. fed conditions is even larger.

Skelly Decl., ¶ 31. In sum, age is much more strongly associated with the pharmacokinetic parameters in the fasted condition than in the fed condition.

Both Core and Mutual also criticize King's use of a meta-analysis, suggesting that the age and gender information that is the subject of King's pending labeling supplement is somehow unreliable. In fact, meta-analyses have been increasingly relied upon by the scientific community and are recognized as valid tools for evaluating quantitative evidence from two or more trials bearing on the same question. Skelly Decl., ¶¶ 50-51. Indeed, FDA has recognized that meta-analyses may provide useful information regarding the safety and efficacy of a

drug product,[14] and has approved package insert language based on the results of meta-analyses.[15] Similarly, FDA has considered meta-analyses in connection with review of proposed health claims and in its recent action on ephedra.[16] The fact is that meta-analyses can provide powerful measures of effects that might otherwise go unnoticed. Certainly it is within FDA's discretion to evaluate and approve truthful labeling statements based on appropriately conducted meta-analyses. Indeed, it is disingenuous for Core and Mutual to argue that King's meta-analysis should be disregarded when they provide no data whatsoever that would contradict the meta-analysis.

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14 *See, e.g., Meta-Analysis: Does it have a role in Drug Development?,* Presentation by Charles Anello, Sc.D., Deputy Director, Office of Biostatistics, CDER (Feb. 2002), available at http://www.fda.gov/cder/Offices/Biostatistics/Anello_328/; *Guidance for Industry M4E: The CTD - Efficacy,* ICH (Aug. 2001), available at: http://www.fda.gov/cber/gdlns/m4ectd.pdf; *Guidance for Industry E9 Statistical Principles for Clinical Trials*, ICH (Sept. 1998), available at: http://www.fda.gov/cder/guidance/ICH_E9-fnl.PDF; *Concept Paper: Premarketing Risk Assessment* (Draft) (March 3, 2002), available at: http://www.fda.gov/cder/meeting/groupIfinal.pdf; 'Dear Doctor' Letter regarding Albumin and Plasma Protein Fraction, available at http://www.fda.gov/medwatch/SAFETY/1998/plasma.htm.

15 *See, e.g.,* approved package inserts for Vioxx® and Celebrex®.

16 *See, e.g.*, 58 Fed. Reg. 2552 (Jan. 6, 1993) (Dietary Fiber and Cardiovascular Disease); 62 Fed. Reg. 3584 (Jan. 23, 1997) (Oats and Coronary Heart Disease); 64 Fed. Reg. 57700 (Oct. 26, 1999) (Soy Protein and Coronary Heart Disease); 69 Fed. Reg. 6788 (Feb. 11, 2004) (ephedra).

IV. Omission Of The Information About Food Effects Would Cause Generic Metaxalone Products To Be Less Safe And Effective Than SKELAXIN®

A. Neither Core Nor Mutual Refute King's Evidence That Practitioners Believe Omission Of The Pharmacokinetic Information From Generic Labeling Will Render Those Products Less Safe And Effective Than SKELAXIN®

The only practitioner to submit a declaration in these proceedings – Dr. Michael E. Elia, M.D. – states that the information in SKELAXIN® labeling describing the relative bioavailability of metaxalone when taken with or without food is critical to prescribers and aids in the safe and effective prescribing and use of SKELAXIN®:

> It is my opinion, however, based on my clinical experience and my personal experience prescribing SKELAXIN®, that the omission of such bioavailability information [concerning the effects of food, age, and gender] from the labeling of generic versions of SKELAXIN® raises serious safety and efficacy concerns and would be highly improper. The information is critical to physicians who prescribe SKELAXIN® or generic versions of SKELAXIN®. . . . [I]t is imperative that the labeling for all metaxalone products include all available information regarding the effects of food, age, and gender on bioavailability. The omission of such information from the labeling of generic metaxalone products would be misleading and could adversely affect the decisions made when prescribing metaxalone to patients. Without the information in the labeling, a prescribing physician would not be able to make an informed decision to determine the dosage amount, frequency, and dosing conditions that will provide optimal patient safety and therapeutic efficacy for an individual patient. Accordingly, the pharmacokinetic information describing the relative bioavailability of metaxalone should appear in labeling for SKELAXIN® as well as labeling for any generic versions of SKELAXIN® marketed in the future.

Elia Decl. 2, ¶¶ 3, 16; *see also id.*, ¶¶ 10, 15; Exhibit 7 to King's March 18, 2004 Citizen Petition, ¶¶ 8, 10-12, 14-15. Dr. Elia further explains that inclusion of this information in the labeling for SKELAXIN® enables him to take it into account to adjust the dosage and administration accordingly and select proper dosage regimens for his individual patients. Elia Decl. 2, ¶¶ 9-12; *see also* Skelly Decl., ¶ 34. For example, depending on the needs and circumstances of his individual patients, in light of the food-effect, Dr. Elia may "recommend that a particular patient dose three times a day with food rather than four times a day without food" and in light of the gender effect, he may "recommend three doses daily to a female patient but recommend four doses daily to a male patient with similar symptoms." Elia Decl. 2, ¶¶ 9, 12.

Finally, Dr. Elia expresses his view that omission of this information from the labeling for generic metaxalone products is misleading and raises serious safety and efficacy concerns. Elia Decl. 2, ¶¶ 3-4; *see also* Exhibit 7 to King's March 18, 2004 Citizen Petition, ¶ 28. As Dr. Elia explains:

> Indeed, it is very misleading if the bioavailability data that is currently required to be included in the labeling for SKELAXIN® is omitted from the labeling for generic metaxalone. In order to obtain FDA's approval, comparative bioequivalence studies showing that branded and generic drugs have the same bioavailability under both fed and fasted conditions are required. However, absent labeling that includes the data demonstrating that there is a significant increase in oral bioavailability in the fed state as compared to the fasted state, a physician would not be able to predict the circumstances under which the bioavailability of generic metaxalone product would be

> equivalent to that of SKELAXIN®. Not knowing the variables or circumstances that might affect drug bioavailability can lead to problems with patient safety and/or treatment efficacy. As such, the omission of information regarding the effects of different variables such as food, age, and gender on the bioavailability of metaxalone in the labeling for generic metaxalone would render the generic product less safe and effective than SKELAXIN®.

Elia Decl. 2, ¶ 6.

Dr. Elia's concerns about the misleading nature of incomplete generic labeling are consistent with FDA's previously stated views. Specifically, FDA has concluded that omission of certain pharmacokinetic information from prescription drug labeling would be misleading:

> The Commissioner disagrees with these comments. Prescription drug labeling should, if possible, provide practitioners with the kind of information they may find valuable for the safe and effective use of drugs. If such information is unknown or unavailable for a drug, the labeling should properly include a statement to that effect. The regulation does not demand that such information be obtained; rather, it requires that labeling either include the information if it is available or include a statement concerning its unavailability. The Commissioner does not believe that the statement would mislead physicians, but the failure to include any reference to that information would itself be misleading.

44 Fed. Reg. 37434, 37442 (June 26, 1979) (discussing requirement that labeling include a statement that the pharmacologic mode of action is unknown or that important human metabolic or pharmacokinetic data are unavailable); *see also* 44 Fed. Reg. 37434, 37442 (June 26, 1979) (pharmacokinetic "information is important, and therefore properly included in prescription drug labeling, if

practitioners would find it to be of value in the safe and effective use of the drug").

In sum, there is no question that the information is properly included in the labeling for SKELAXIN® and cannot be omitted from the labeling for generic metaxalone products without rendering them less safe or effective than SKELAXIN®. 21 C.F.R. § 314.127(a)(7).[17]

Relying on its expert, Core dismisses Dr. Elia's opinions, arguing that it is impossible for a clinician to adjust the dosage and administration of metaxalone because there are no known effective or toxic plasma concentrations for a clinician to seek to achieve or avoid. Core's assertion reflects a naïve and simplistic view of the considerations that inform a prescribing physician's choice of dosage and administration instructions for their patients. A physician need not be "aiming" for

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17 Citing a 1979 Federal Register Notice, Core claims that it is improper to base statements in drug labeling on the views of one physician. The quote upon which Core relies is an excerpt from FDA's response to a comment urging that *in vitro* data for anti-infective drugs not be accompanied by the disclaimer to the effect that, "their clinical significance is unknown." FDA explained that statements about drug efficacy are to be based on adequate and well-controlled clinical investigations, and therefore, despite physicians' positive experiences with anti-infective drugs, the disclaimer is needed. The Federal Register discussion does not speak to the issue of whether, when considering the significance of certain clinical data to practitioners, the views of a doctor who frequently prescribes the drug are informative. Clearly they are and Core has failed to submit any data that would contradict Dr. Elia's views. Indeed, in the absence of contrary data of the type that would be necessary to justify the omission of PK information from the metaxalone labeling, neither Core nor FDA are in a position to ignore the expert opinion of the prescribers who rely on the information provided in drug labeling to appropriately treat their patients. The burden is on Core and Mutual to provide the data necessary to establish the propriety of their proposed label carve-outs.

a specific numerical plasma concentration when adjusting dosage and administration to take individual patients' responses and needs into account.

Dr. Benet explains the logical flaws in Core's position that the lack of information correlating safety or efficacy of metaxalone with plasma concentration levels renders the food effect information clinically irrelevant as follows:

> Such a conclusion suggests that Core's expert would thus logically argue that unless a correlation between plasma concentrations and safety and efficacy exists, there would be no basis for recommending a dose of a drug. When a food effect changes plasma concentrations, that result is equivalent to changing the dose. The listing of food effect data in the package insert is included to give clinicians information concerning the "available dose". This then gives the clinician relevant information that he/she chooses to use or not use based on his/her clinical experience with the drug.

Benet Decl. 2, ¶ 11.

Moreover, Core and Dr. Bass err in assuming that because information about the relationship between the safety and/or efficacy of metaxalone and plasma concentration levels is currently lacking, there is no such relationship. Building on this error, Core and Dr. Bass wrongly further presume because there is allegedly no such relationship, the differences in fed and fasted bioavailability do not correlate to any therapeutic effect and have no clinical significance. As Dr. Benet explains, the lack of information about the relationship between safety and efficacy and plasma concentration levels simply does not establish clinical insignificance. Benet Decl. 2, ¶¶ 12-13.

Finally, if Core is correct, food effect studies should not be conducted on, and all pharmacokinetic information should be omitted from the labeling of, all drugs for which safety and efficacy have no known correlation to their plasma concentration levels. FDA has never taken this position and instead (1) recognizes that regulatory judgments are properly based on the understanding that "some relationship exists between the efficacy/safety and concentration of active moiety and/or its important metabolite or metabolites in the systemic circulation,"[18] and (2) requires fed studies (single-dose, high-fat) on all orally administered new chemical entities and most orally administered generic drugs.[19] Indeed, food effect studies are described in the labeling for all three of the drugs identified by Core's expert (*see* Bass Decl., ¶ 38) as similar to metaxalone in that their safety and efficacy also have no known correlation to their plasma levels. *See* approved package inserts for Nexium®, Fosamax®, and Prempro™; Benet Decl. 2, ¶¶ 13-14.

Core also claims that information in SKELAXIN® labeling describing the relative bioavailability of metaxalone when taken with or without food has no

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18 *See Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations,* CDER at 6 (March 2003), available at: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3995B1_07_GFI-BioAvail-BioEquiv.pdf.

19 *See Guidance for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies,* CDER at pp. 3-4 (Dec. 2002), available at: http://www.fda.gov/cder/guidance/5194fnl.doc.

bearing on safety or efficacy because "none of this information requires a dosing adjustment." Core appears to labor under the misimpression that the only important portion of a package insert is the Dosage and Administration section, and the remaining information is superfluous and may be omitted. Of course, FDA's regulations reflect a contrary view, and require a host of additional information beyond the Dosage and Administration section. *See* 21 C.F.R. §§ 201.56, 201.57. Physicians also rely upon sections of drug labeling beyond the Dosage and Administration section:

> As discussed above and in my original declaration, the information provided in a drug's labeling is the single most important source from which a prescribing physician can determine whether and how that drug is to be dosed and administered. In addition to information in the "Dosage and Administration" section of a drug label, physicians also rely on other sections of the labeling to provide important information such as conditions that may affect drug bioavailability, which is necessary to consider in choosing, among other things, appropriate doses and in providing appropriate dosing instructions to the patient.

Elia Decl. 2, ¶ 14.

Indeed, FDA has repeatedly approved labeling including information of unknown clinical significance that does not result in a change to the Dosage and Administration section of labeling. *See* Citizen Petition, pp. 20-22. Moreover, Core again supplies an answer to the wrong question. The question is not whether the information "requires" a dosing adjustment, but, rather, whether practitioners can use the information to make

adjustments suitable for individual patients, thereby potentially enhancing the safe and effective use of the product. As the Agency has recognized, food effect information is important and may be used by practitioners, even if specific dosing instructions are not provided in the Dosage and Administration section of a package insert: "Altered BA of drug products can lead to dosage adjustments or, more commonly, to the provision of specific dosing instructions in relation to administration with meals."[20]

B. Core and Mutual's Unsupported, Speculative Theories Do Not Establish That King's Data Are Clinically Irrelevant

Core and Mutual's attempts to convince the Agency – without submitting any supporting data of their own – that King's studies generated only clinically irrelevant information do not stop with their attempt to discredit Dr. Elia's opinions. They also offer various additional unsupported arguments, the flaws in which are discussed below.

Core argues that information describing the relative bioavailability of metaxalone when taken with or without food must be irrelevant because the difference between fed and fasted bioavailability is less than the 33% variation reflected in the approved dosing schedule, which allows three to four 800 mg tablets a day. This assertion makes no sense unless one assumes that all doses of a

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20 See Reports and guidance documents; availability, etc.: Food-effect bioavailability and bioequivalence studies; industry guidance, 62 Fed. Reg. 67879 (Dec. 30, 1997).

drug are clinically equivalent – a counter-intuitive assumption that Core, once again, presses on FDA in the total absence of any supportive data. Moreover, Core's assertion relies on an unrealistic and inappropriate view of the practice of medicine in a strained effort to support its position. It is safe to assume that prescribing physicians appreciate that the fewer tablets taken per day, the lower the exposure to a drug, even if this fact is not expressly stated in the labeling for a drug. Presumably, practitioners take this basic maxim into account when determining whether to prescribe three or four SKELAXIN® tablets a day for their individual patients, or to prescribe SKELAXIN® for less frequent use when warranted. Currently, physicians can also take into consideration the food effect information provided in SKELAXIN® labeling when making dosage and administration determinations.

If, however, the food effect information is omitted from the labeling for generic metaxalone, physicians reading the incomplete labeling[21] are likely to conclude either that the fed and fasted bioavailability of metaxalone is the same or that the effects of food on the bioavailability of metaxalone are unknown. Elia

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21 Core's contention that its labeling text is irrelevant because it will not distribute its labeling to practitioners is telling. In essence, Core argues that it should be permitted to ignore Hatch-Waxman labeling requirements because it will not show its labeling to anyone. Essentially, Core *is* adopting the SKELAXIN® labeling verbatim as a practical matter, but is seeking to omit parts of it from its own label solely to attempt to circumvent the consequences of infringing King's patent. Congress' intent to balance competing interests through the Hatch-Waxman amendments requires that this position be summarily rejected.

Decl. 2, ¶ 5; Exhibit 7 to King's March 18, 2004 Citizen Petition, ¶ 18. Such a physician would most likely conclude that there was no need to adjust dosage or administration to account for changes in bioavailability due to food effects. Exhibit 7 to King's March 18, 2004 Citizen Petition, ¶ 18. As Dr. Elia explains, this erroneous assumption could lead to sub-optimal dosing strategies and could negatively impact the outcome of drug therapy. Exhibit 7 to King's March 18, 2004 Citizen Petition, ¶ 18; Elia Decl. 2, ¶ 5. In sum, the issue is not whether the magnitude of the variability exceeds a certain threshold, but rather, whether the variability, whatever its magnitude, is disclosed so that physicians can consider it when making decisions for their individual patients.

In any event, if Core's position were accepted, all information concerning bioavailability of a drug when taken with or without food (even if bioavailability is unchanged) should be considered irrelevant and should be omitted from the labeling of drugs that are available in multiple strengths, particularly when the permissible variation in dose exceeds any observed difference between fed and fasted bioavailability. Such a radical policy change would necessitate changes in the labeling for many drugs that are available in multiple strengths, including Paxil®, Requip®, Diovan®, OxyContin®, Adderall®, Effexor®, Plendil®, Seroquel®, and Glucovance®.

Mutual also argues that King's data should be ignored because King's

studies did not measure safety, side effects, or other clinical endpoints. Contrary to Mutual's suggestion, this is not a deficiency in King's studies. Most food effect studies do not measure clinical endpoints. Benet Decl. 2, ¶ 15; Skelly Decl., ¶ 37; *see Guidance for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies,* CDER (Dec. 2002). Indeed, bioavailability and bioequivalence studies that do not measure clinical endpoints are routinely conducted and data generated from such studies are included in product labeling. Skelly Decl., ¶ 37; *see Guidance for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies,* CDER (Dec. 2002). Without proof, Mutual's argument amounts to speculation:

> [I]t cannot be presumed that because the King's studies only measured blood plasma levels of metaxalone, that the resulting pharmacokinetic data are clinically irrelevant. At the very least, blood levels have clinical relevance to the extent that a drug such as metaxalone must reach the blood in order to have clinical effect. Changes in blood level can be an indication that there will be changes in pharmacologic effect. In fact, the bioavailability of an orally administered drug product with a systemic clinical effect is critical to such effect. Certainly, I am not aware of any scientific data that support an assertion that blood levels of metaxalone do not assure a clinical effect. Thus, in the absence of clinical evidence that there is no nexus between the blood levels of Skelaxin® and its clinical safety or efficacy, there is no scientific basis for assuming that the pharmacokinetic data are immaterial to determining safe and effective use of Skelaxin®.

Skelly Decl., ¶ 40. Dr. Benet echos Dr. Skelly's comments, noting that even the reference upon which Mutual relies notes that the bioavailability

and clinical effect of most drugs do correlate. Benet Decl. 2, ¶ 16.

Moreover, the bioequivalency studies that generic drug companies such as Mutual submit in support of their applications measure only blood levels, not clinical effect. Skelly Decl., ¶ 37; Benet Decl. 2, ¶ 16; *see Guidance for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies,* CDER (Dec. 2002). The tension in Mutual's position is readily apparent:

> Mutual also fails to mention that an asserted lack of correlation between blood levels and clinical effect would undercut the basic assumptions that underlay the approval of generic drugs that have been tested only for bioequivalence to a reference listed drug and have never been tested – other than in blood level comparisons – for clinical efficacy and safety.

Benet Decl. 2, ¶ 16. As was the case with Core's argument on individual subject data (*see* Section II.B. above), we are certain that Mutual does not intend to convince the Agency to require safety and efficacy studies for approval of generic metaxalone products. The fact that Mutual would make this argument, however, underscores the degree to which it – like Core – chooses to overlook the blatant inconsistencies in its position.

V. Generic Applicants Have The Burden Of Proving That Omission Of The Information About Food Effects Would Not Cause Generic Metaxalone Products To Be Less Safe And Effective Than SKELAXIN®

The FDCA provides that an ANDA applicant has the burden of establishing

that the labeling it proposes to use for its generic product is the same as the labeling approved for the RLD, and thus, that any deviations from that approved labeling fall into the limited exceptions to that requirement. 21 U.S.C. § 355(j)(2)(A)(v). Core, as the party seeking approval of a drug product with 'inequivalent' labeling, has the burden of proving that the changes it proposes will not cause its product to be less safe and effective than SKELAXIN®.[22] FDA regulations expressly state that the Agency may refuse to approve Core's ANDA if the information submitted in it is insufficient to show either that Core's proposed labeling is the same as that approved for SKELAXIN® or that any proposed differences do not render Core's proposed generic product less safe or effective than SKELAXIN®. 21 C.F.R. § 314.127(a)(7).[23]

Should FDA refuse to approve Core's ANDA, on this or any other grounds, Core may challenge that decision by seeking a hearing. 21 C.F.R. § 314.125. If a

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22 In this regard, Core mischaracterizes King's position. King has never argued that, by proffering data, it imposed a burden on those seeking to market generic metaxalone to show that the data are irrelevant to the safe and effective use of the drug. However, once pioneer labeling is approved, after FDA review and evaluation of the underlying data, the generic applicant bears the burden of proving that omission of any aspect of this approved labeling would not render the generic product less safe and effective than the pioneer product.

23 Core cites the 1992 preamble to FDA's final regulations concerning ANDAs in support of its comments (*see* pp. 14-15). While the discussion appears unrelated to Core's position, the preamble discussion does state that generic applicants may be required to submit data in support of certain labeling changes. 57 Fed. Reg. 17950, 17961-62 (April 28, 1992). This refutes Core's position that the burden of proof rests with the pioneer, and accordingly, deviations from the approved RLD labeling are permissible, unless proven by the pioneer to negatively impact safety or efficacy.

hearing is granted, Core will have the burden of proof. *See* 5 U.S.C. §§ 554, 556. Simply stated, the burden of proof is never on FDA (or on other drug companies) to justify the Agency's refusal to approve a drug product; instead, the burden is always on the applicant. Here, the applicant – Core – has failed to satisfy its burden.

Core's attempt to shift its burden to King via an analogy to bioequivalency testing also fails. Core argues that King must refute Core's request for approval of 'inequivalent' labeling because pioneer companies have the burden of disproving a generic company's showing of bioequivalence. Assuming *arguendo* that, once a generic applicant submits data satisfying FDA bioequivalence criteria, the burden falls on the pioneer to refute that showing with contrary data,[24] this proposition still does not in any way support Core's position that it is automatically entitled to approval of 'inequivalent' labeling unless King makes an affirmative showing that such labeling is inappropriate. In the former case posited by Core, bioequivalency has been established by the generic company and the burden to disprove this showing then shifts to the pioneer. Here, in contrast, Core has not established either that its labeling is the same as the labeling for SKELAXIN® or that the changes it proposes do not render its product less safe and effective than

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24 King notes, however, that Core's quotation from one member of the Advisory Committee on Pharmaceutical Science hardly establishes this proposition.

SKELAXIN®. Core instead requests that the Agency *assume* that inequivalent labeling does not render its generic product less safe or effective than SKELAXIN®. Accordingly, there is nothing for King to "disprove." Core's analogy would support its position only if the Agency also *assumed* that a generic product is bioequivalent to a pioneer product, unless the pioneer company submits data proving inequivalence.

Finally, were the burden allocated as Core claims, a generic applicant could rewrite any part of any label in any way it pleased (as long as it is trying to avoid a patent infringement claim or exclusivity) and it would be entitled to approval unless the pioneer happened to have conducted studies that directly contradict the propriety of the changes the generic applicant proposes. Presumably, FDA would need to establish a procedure whereby pioneers are formally notified of proposed labeling carve-outs and invited to submit data showing the proposed generic labeling would render the generic product less safe or effective. Such a policy amounts to an invitation for chaos in drug labeling that turns the Hatch-Waxman same-labeling requirement on its head.[25]

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25 Core argues that King's new, approvable labeling could also be carved out - apparently based on its contrary opinion, backed by no studies of its own, that the information is wrong. This assertion underscores the fact that FDA, and not generic drug industry, is properly responsible for reviewing and approving drug labeling and confirms the propriety of the approach adopted through the Hatch-Waxman amendments requiring generic drug makers to copy the pioneer's labeling verbatim, lest they decide to rewrite the labeling to suit themselves.

VI. Summary Reversal Of The Agency's Prior Position, Under Which Generic Metaxalone Products Were Not Permitted To Omit The Bioavailability Information At Issue, Violates The APA And The Agency's Good Guidance Practices Regulations

In its Comments, Core asserts that FDA's March 1st Letter was not a reversal of policy because FDA's initial inclusion of Elan's pharmacokinetic data in the labeling for Skelaxin® "did not rise to the level of a 'policy' in the first place." King has never argued that FDA reversed its decision to include Elan's pharmacokinetic data in the labeling for Skelaxin®. Indeed, these data continue to be included in the labeling for Skelaxin®.[26] Rather, it is King's position that FDA's March 1st Letter was a dramatic reversal of the Agency's prior position to consistently require generic metaxalone applicants to file patent certifications to the '128 patent, acknowledging that the use of metaxalone protected by that patent cannot appropriately be removed from the labeling for the generic products.[27]

Core also repeatedly claims that the March 1st Letter was not a reversal of FDA's position because it is "entirely consistent with the caveat it previously

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26 Of course, were FDA to issue a final determination permitting omission of this information from the labeling for generic metaxalone products, the Agency would have no legal basis to require King to retain that information in the labeling for SKELAXIN®.

27 Although Core acknowledges that "ANDA applicants were not permitted to provide . . . a section viii statement" on the '128 patent and FDA's March 1st Letter similarly indicates that FDA initially decided not to permit ANDA applicants to carve out of their labeling the food effect information, FDA's initial determination is not currently part of this docket. FDA's decision and its supporting rationale are clearly relevant to King's Petitions, and therefore King requests that the Agency place that decision, and any supporting materials, in the docket.

included in the labeling for SKELAXIN® that the 'clinical relevance of these effects is unknown.'" This is simply fallacious. The fact that the clinical relevance of the difference between fed-state and fasted-state bioavailability may be "unknown" does not lead to the conclusion that the available information about bioavailability does not have clinical significance or that the information that is known can or should (or must – if it is omitted) be ignored in making prescribing decisions. Likewise, the fact that the SKELAXIN® labeling states that the clinical relevance of the information is unknown does not in any way support the position that deleting this information from the generic labeling would not render the products "less safe or effective than the listed drug," 21 C.F.R. § 314.127(a)(7), the standard of proof that the generic applicant must meet in order to carve this information out of the labeling.

A. FDA's Dramatic Reversal Of Policy Embodied In The March 1st Letter Violates The APA

In its March 1st Letter, FDA abruptly reversed its previous position that, under 21 C.F.R. § 314.127(a)(7), generic metaxalone applicants may not omit the fed-state bioavailability information covered by the '128 patent from the labeling of their products. Courts have held that when an agency has given its regulation a definitive interpretation, and later changes that interpretation, the agency has in fact amended its rule, which cannot be accomplished without notice and comment. *Alaska Professional Hunters Ass'n v. FAA*, 177 F.3d 1030 (D.C.Cir.1999);

Paralyzed Veterans of America v. D.C. Arena, 117 F.3d 579 (D.C.Cir. 1997); *Shell Offshore Inc. v. Babbitt*, 238 F.3d 622 (5th Cir. 2001). This is particularly the case where, as here, regulated industry substantially relied on the agency's prior position.

Under very similar facts as those presented here, the D.C. Circuit held that agency action that reverses a previous interpretation of a regulation without notice and comment violates the APA. In *Alaska Professional Hunters*, Alaskan fishing and hunting guides challenged a Federal Aviation Administration ("FAA") notice that required guides to comply with FAA regulations applicable to commercial air operations. The notice abruptly reversed the agency's previous position, set forth in an adjudication, that guides need not comply with commercial pilot regulations. In its opinion, the D.C. Circuit stated that "[w]hen an agency has given its regulation a definitive interpretation, and later significantly revises that interpretation, the agency has in effect amended its rule, something it may not accomplish without notice and comment." 177 F.3d at 1034; *see also Syncor International Corp. v. Shalala*, 127 F.3d 90, 94 (D.C.Cir. 1997) (a modification of an interpretative rule construing an agency's substantive regulation "will likely require a notice and comment procedure").

In the *Alaska Professional Hunters* opinion, the court highlighted the fact that the Alaskan guide pilots and lodge operators relied on the FAA's previous advice,

opening lodges and building up other business in reliance on the FAA's position that their flights were not governed by the commercial pilot regulations. Here, as in *Alaska Professional Hunters*, the parties have made significant investments in reliance on FDA's previous interpretation of its regulations. Based on FDA's prior position, a number of parties have filed applications and certifications and have begun resolving the relevant patent issues in an orderly fashion as envisioned by Hatch-Waxman. As a result, patent litigation has been ongoing for eighteen months. The sequence of those filings has also resulted in first-to-file status and potential eligibility for 180 day exclusivity for one ANDA applicant. Therefore, FDA's change in position in the March 1st Letter will result in a substantial upheaval in the expectations and rights of virtually all of the interested parties.[28] As a result, it may not be adopted without notice and comment under the APA.

Furthermore, the new policy announced in FDA's March 1st Letter "runs counter to the evidence before the agency," and therefore is arbitrary and capricious and must be overturned. *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). In particular, courts have consistently held that an abrupt change in course by an agency must be supported by reasoned

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28 We also point out that King purchased the SKELAXIN® product and NDA from Elan in 2003, when FDA's position had been clearly stated and appeared to be entirely consistent with past FDA practice and applicable legal precedents, ANDA applicants had already made filings in accordance with that position, and the process of patent litigation had already begun.

analysis. *See, e.g., Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 42 ("an agency changing its course by rescinding a rule is obligated to supply a reasoned analysis for the change"); *National Black Media Coalition v. FCC*, 775 F.2d 342, 355-56, 356 n.17 (D.C.Cir. 1985) (agency must offer sufficient explanation to ensure court that it is not "repudiat[ing] precedent simply to conform with a shifting political mood") (citing cases); *Brae Corp. v. United States*, 740 F.2d 1023, 1038 (D.C.Cir. 1984) (agency must explain why the original reasons for adopting the rule or policy are no longer dispositive), *cert. denied*, 471 U.S. 1069 (1985). FDA has failed to provide a sufficient factual, legal, and scientific basis for its significant departure from its prior position in this case. Accordingly, the conclusions in its March 1st Letter are arbitrary and capricious in violation of the APA.

As noted above, FDA's violation of the APA in this instance is particularly egregious because the Agency's policy change completely alters the rights and obligations created under FDA's previous guidance. Indeed, FDA has acknowledged the potential implications of such an agency action in its preamble to the proposed rule on patent listing requirements and application of 30-month stays: "If we were to adopt an alternative implementation plan, we would risk upsetting legitimate expectations held by those who had relied on our earlier interpretation of the act." 67 Fed. Reg. 65448, 65457 (Oct. 24, 2002); *see also* 68 Fed. Reg. 36676, 36696 (June 18, 2003). The sudden reversal of FDA's prior

position based on the March 1st Letter will significantly damage those parties who have relied upon it and may significantly affect the interests of the pharmaceutical industry, prescribers and the public at large. Under the APA, policy changes of such magnitude may not be implemented by an agency without providing prior notice and an appropriate opportunity for comment, and a reasoned analysis supporting any final decision to implement a change in course.

B. The Dramatic Reversal Of Policy Embodied In The March 1, 2004 Letter Violates FDA's Good Guidance Practices Regulations

Although the March 1st Letter may have been directed to an individual person or firm, the position stated in the letter constitutes a Level 1 guidance document under FDA's Good Guidance Practices ("GGP") Regulations because it sets forth "changes in interpretation or policy that are of more than a minor nature," raises "complex scientific issues," and "cover[s] highly controversial issues" that will have a significant impact upon regulated industry as a whole. *See* 21 C.F.R. § 10.115(c)(1).

In its recent decision concerning generic ribavirin products, FDA took the position that communications with generic drug applicants cannot constitute guidance documents. *See* April 6, 2004 Letter, Docket 2003P-0321.[29] However,

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29 Core misstates the ribavirin precedent. In fact, FDA's decision does not support Core's position. In the case of ribavirin, the alleged risk of dosing error specifically related only to the use of the drug with PEG-Intron – the precise use that the generic applicants proposed to carve out of their labeling. Once it was determined that the use with PEG-interferon could be carved

FDA has clearly acknowledged that the Agency "may not use documents or other means of communication that are excluded from the definition of a guidance document to informally communicate new or different regulatory expectations to a broad public audience for the first time [and that] GGPs must be followed whenever regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public audience." 21 C.F.R. § 10.115(e); *see also* 21 U.S.C. § 371(h)(1)(C) ("For guidance documents that set forth initial interpretations of a statute or regulation, changes in interpretation or policy that are of more than a minor nature, complex scientific issues, or highly controversial issues, the Secretary shall ensure public participation prior to implementation..."); CDRH Manual for the Good Guidance Practices (GGP) Regulations; Final Guidance for FDA Staff at 3 (stating that FDA may not use means other than a guidance document to communicate new policy or new regulatory approaches).

In the March 1st Letter, FDA takes the position that "[b]ecause the clinical effect of the increased bioavailability is unknown, omission of fed-state bioavailability information from the labeling will not render the drug less safe [or

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out, there was arguably no need for the generic labeling to provide dosing information that related solely to the carved-out use, even though that might be theoretically confusing. Here, the pharmacokinetic information in the SKELAXIN® labeling relates to the only approved use of metaxalone and that use cannot and is not proposed to be carved out.

effective] for its approved uses." As explained above and in King's Citizen Petition (pp. 20-22), this position – that all information whose clinical significance is unknown may be omitted from drug labeling – is unprecedented and has broad applicability well beyond the case of metaxalone. Accordingly, the March 1st Letter cannot be categorized as a mere communication with an individual person or firm, but rather must be viewed as a significant change in interpretation and policy. As such, FDA must follow the procedural requirements set forth in the GGP regulations for a Level 1 guidance, including publishing a notice in the Federal Register announcing the availability of a draft guidance document, inviting comments on the draft guidance document, and reviewing the comments received. 21 C.F.R. §§ 10.115(g)(1)(ii), (iv).

VII. King's Petition for Stay Satisfies The Criteria For Both A Mandatory And A Discretionary Stay

Core argues that King has failed to identify any legitimate private or public interest in support of its Petition for Stay, dismissing the Petition as revealing King's 'true motives.' Core's accusations are nothing more than empty rhetoric. Contrary to Core's suggestion, there is nothing nefarious about King's desire to preserve its legally appropriate, exclusive sales position. And it is well settled that the type of competitive injuries identified in King's Petition as flowing from an

improper erosion of such an exclusive sales position can constitute irreparable harm.[30]

With respect to the public interest and public policy, King has demonstrated, in its Citizen Petition and in this and other additional docket submissions, that omission from generic labeling of information about the relative bioavailability of metaxalone when taken with or without food would render those generic products less safe and effective than SKELAXIN®. Approval of such a drug product clearly harms both physicians and consumers, and therefore the public interest and public policy are served by granting King's Petition. In addition, granting King's Petition for Stay would: (1) help effectuate the goal of the Hatch-Waxman amendments to encourage research and innovation;[31] (2) allow patent issues to be resolved via the orderly procedure (already underway) created by the Hatch-Waxman amendments without disrupting settled expectations; (3) permit all interested parties to comment on the dramatic and broadly applicable potential change in policy reflected in the March 1, 2004 letter; and (4) serve the

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30 *See Bracco Diagnostics, Inc. v. Shalala,* 963 F.Supp. 20, 29 (D.D.C. 1997); *Purdue Pharma L.P. v. Boehringer Ingelheim GMBH,* 237 F.3d 1359, 1367-68 (Fed. Cir. 2001); *Allergan, Inc. v. Shalala,* 6 Food and Drug Rep. 389, 391, No. 94-1223 (D.D.C. Nov. 10, 1994) (Greene, J.).

31 *See Collagenex Pharmaceuticals, Inc. v. Thompson,* 2003 U.S. Dist. LEXIS 25229 at *35 (D.D.C. July 22, 2003) (recognizing the public's interest in encouraging drug research and development and concluding that "the barriers to competition that Congress has erected are in the public interest because they encourage the development of innovative drugs by ensuring a period of market exclusivity").

public's interest in faithful application of the laws.[32] For these reasons, both private and public interests support King's Petition for Stay.

VIII. The Fed Dosing Instruction Proposed In King's Pending Labeling Supplement Is Appropriate

While Mutual's primary position seems to be that the review division should reverse its previous decision and refuse to approve King's pending labeling supplement, Mutual also offers a backup position: if food-related dosing and administration instructions are to be added to the labeling for SKELAXIN®, the instruction should be to take metaxalone on an empty stomach. Mutual claims that food effects are highly dependent upon specific food composition, and therefore, to preclude variability in plasma concentrations caused by different foods, a fasted dosing instruction is appropriate.

Mutual's "evidence" that the bioavailability of metaxalone will vary depending on meal composition consists solely of studies on *other drugs* whose bioavailability differs when co-administered with meals of different fat content. None of these studies provides any information on the bioavailability of metaxalone, much less information showing that the bioavailability of metaxalone materially varies when it is co-administered with different types of meals. Benet Decl. 2, ¶¶ 18-22. Absent data – which neither Mutual nor Core seem willing or

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32 *See Bracco Diagnostics, Inc. v. Shalala,* 963 F.Supp. 20, 30 (D.D.C. 1997).

able to provide – any contention that co-administration of metaxalone with meals other than the standard high-fat breakfast used in King's studies will produce different plasma concentrations of metaxalone is purely speculative. Skelly Decl., ¶ 46; Benet Decl. 2, ¶¶ 18-22.

Accordingly, there is no known meal-composition-related variability to preclude and Mutual's contention that a fasted dosing instruction is needed to address this supposed variability is baseless. In the words of Dr. Benet:

> [B]oth Core and Mutual fail to identify any evidence from clinical studies demonstrating that the fed-state bioavailability of metaxalone would be affected by different types of food. Absent any such data, it is impossible to conclude that composition of the meal administered would affect the bioavailability of metaxalone in the fed state. Instead, the assumptions made by both Core and Mutual are based on irrelevant references reporting the effects of different types of meals on the bioavailability of drugs other than Skelaxin®. Such studies provide no information on the bioavailability of metaxalone. . . . Even though Mutual has no actual data to support its arguments that co-administration with various types of meals would affect the blood levels of metaxalone differently, Mutual relies on its presumption that there will be variation in fed-state bioavailability based on food constitution to make yet another presumption: Mutual suggests that dosing on an empty stomach would remove any effect of meal-to-meal variation and the purported resulting variation in bioavailability. As discussed above, there is no basis for Mutual to conclude that co-administration with meals other than the standardized high-fat meal used in the Skelaxin® bioavailability studies would result in variability in plasma concentration levels, much less to conclude that dosing on an empty stomach would prevent the theorized variations in blood levels of metaxalone.

Benet Decl. 2, ¶¶ 18-21.

In contrast, King has submitted data from clinical studies conducted with

metaxalone to support its proposed fed dosing instruction. Specifically, King's meta-analysis shows that, in the fasted state, bioavailability is statistically significantly increased with an increase in age and, in the fed state, age has little or no effect upon the bioavailability of SKELAXIN®. Thus, King's proposed fed dosing instruction reduces one variable known to impact metaxalone bioavailability: administration with food will result in more consistent plasma levels of metaxalone across age groups. The proposed fed dosing instruction provides useful information to practitioners, as Dr. Elia explains in his declaration:

> As I discussed in my original declaration, it is of particular relevance to my practice to know that in the absence of food, as age increases, so does bioavailability of SKELAXIN®, whereas age has little or no effect upon the rate and extent of absorption of SKELAXIN® when administered with food. The ability to minimize at least one variable that affects bioavailability of SKELAXIN® by administering it with food is very useful in determining particular dosage regimens for my diverse population of patients. With this information available to me, I would be able to at least minimize any age-related variations in the bioavailability of SKELAXIN® by recommending its co-administration with food.

Elia Decl. 2, ¶ 11.

Moreover, King's proposed fed dosing instruction would presumably reduce the supposed variability associated with the enhanced digestive functions described by Core and its expert. According to Core and Dr. Bass, King's data indicate that fasted state bioavailability can equal or exceed fed state bioavailability when metaxalone is administered at a time that happens to coincide

with secretion of bile into the duodenum associated with Phase III of the migrating motor complex ("MMC"). Although Dr. Bass provides no data indicating this actually occurs with metaxalone, assuming that it is true that this enhanced digestive process occurs only in the fasted state, patients taking metaxalone on an empty stomach may or may not experience the increased bioavailability Dr. Bass describes each time the drug is administered because there is no way to ensure that patients take metaxalone during any particular phase of the MMC. *See* Skelly Decl., ¶ 19 ("Finally, assuming *arguendo* that this gastric phenomena exists, knowledge that Phase III of the MMC occurs when fasting and that administration of metaxalone (or any other drug) during this phase may enhance bioavailability cannot be used by practitioners to determine proper dosage and administration because it is impossible to predict exactly when the enhanced digestive process will occur, so there is no way for patients or their physicians to ensure that drug products are taken at a time that coincides with Phase III of the MMC"). Thus, administration with food would presumably avoid this purported variability and unpredictability and result in more consistent plasma levels of metaxalone.

IX. FDA Review of King's Labeling Supplement Should Not Be Stayed Nor Should the FDA Review Process be Open to the Public

As set forth in King's May 13, 2004 Comments on Mutual's Petition for Stay, Mutual has failed to satisfy the criteria for a mandatory or a discretionary stay of approval of King's approvable labeling supplement. Nothing contained in Mutual's May 17, 2004 Supplemental Submission adds any further support for its request for a stay. Mutual's sole justification for its requested stay is to permit it and others unprecedented access to confidential information in King's NDA and the opportunity to interfere in and delay FDA's evaluation of that material.

There is simply no legal basis for Mutual's demand for access to this proprietary data. It is well established that these data are not available for public disclosure. *See* 21 C.F.R. §§ 314.430, 20.61; 5 U.S.C. 552(b)(4); 21 U.S.C. § 355(l). Nevertheless, Mutual argues that King has somehow "opened the door" to public debate of the studies through the filing of its Citizen Petition. In fact, as explained in King's May 13, 2004 submission, King's Citizen Petition pertains to the propriety of omitting from generic labeling pharmacokinetic information added to the labeling for SKELAXIN® *over two years ago*. That Petition demonstrates that the pharmacokinetic information in the *currently approved* SKELAXIN® labeling cannot be omitted from the labeling for generic metaxalone without rendering those generic products less safe or effective for their conditions of use. Mutual, in its Petition for Stay and Supplemental Submission, is the *only* party that

is relying on the data in King's pending supplement. Neither Mutual's attempted use of those data nor King's identification of the flaws in Mutual's reasoning (*see* Section VIII. above) provide any basis to disclose King's proprietary data to the public. Thus, contrary to Mutual's assertions, FDA can – and indeed must – grant King's Petitions without making the full data and reports of all of King's metaxalone studies available for public review and comment.

Conclusion

Core's submission, while lengthy, is devoid of any actual clinical data demonstrating that omission of information concerning the relative bioavailability of metaxalone when taken with or without food from its product label will not render that product less safe or effective than SKELAXIN®. Absent such a showing, the Commissioner must (a) rescind the March 1, 2004 Letter issued by the Director of OGD; (b) require applicants seeking approval to market generic metaxalone products that rely on King's SKELAXIN® as the RLD to submit a patent certification pursuant to 21 U.S.C. § 355(j)(2(A)(vii) on U.S. Patent No. 6,407,128; and (c) prohibit the removal from generic metaxalone labeling of the pharmacokinetic information that appears in the SKELAXIN® labeling.

EXHIBITS

Similarly, Mutual has submitted no data or other evidence to support its request for a stay and reversal of FDA's decision regarding King's approvable labeling supplement. Accordingly, Mutual's Petition for Stay should be denied.

Respectfully submitted,

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